SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Silicone Gel-Filled Breast Implants

Device Trade Name: Mentor Silicone Gel-Filled Breast Implants

Applicant: Mentor Corporation
201 Mentor Drive
Santa Barbara, California 93111

Premarket Approval (PMA) Application Number: To be determined

Date of Panel Recommendation: To be determined

Date of Good Manufacturing Practice Inspection: To be determined

Date of Notice of Approval to Applicant: To be determined

II. INDICATIONS FOR USE

Breast implants are indicated for females for the following indications:

- Breast Augmentation. A woman must be at least 18 years old for breast augmentation.
- Breast Reconstruction.
- Revision

III. CONTRAINDICATIONS

Patient Groups in which the product is contraindicated:

- Women with active infection anywhere in the body.
- Women with existing malignant or pre-malignant breast cancer without adequate treatment.
- Augmentation in women who are currently pregnant or nursing.

Surgical Practices in which product use is contraindicated due to compromise of product integrity:

- Stacking of implants: Do not place more than one implant per breast pocket.
- Do not alter the implant.

IV. WARNINGS

1. ***Closed Capsulotomy***
DO NOT treat capsular contracture by forceful external compression, which will likely result in implant damage, rupture, folds, and/or hematoma.

2. ***Reuse***
Breast implants are intended for single use only. Do not resterilize.

3. ***Avoiding Damage during Surgery***

- Care should be taken not to damage the implant with surgical instruments.
- Do not insert or attempt to repair a damaged implant.
- Use care in subsequent procedures such as open capsulotomy, breast pocket revision, hematoma/seroma aspiration, and biopsy/lumpectomy to avoid damage to the implant shell.
- Do not contact the implant with disposable, capacitor-type cautery devices.

4. ***Microwave Diathermy***

The use of microwave diathermy in patients with breast implants is not recommended, as it has been reported to cause tissue necrosis, skin erosion, and extrusion of the implant.

5. Do not use endoscopic placement or periumbilical approach in placement of the implant.

V. PRECAUTIONS

1. ***Specific Populations***

Safety and effectiveness has not been established in patients with:

- Autoimmune diseases such as lupus and scleroderma.
- A compromised immune system (e.g., currently receiving immunosuppressive therapy).
- Patients with conditions or medications which interfere with wound healing ability (such as poorly controlled diabetes) or blood clotting (such as concurrent coumadin therapy).
- Reduced blood supply to breast tissue.

2. ***Mammography***

Breast implants may complicate the interpretation of mammographic images by obscuring underlying breast tissue and/or by compressing overlying tissue. Accredited mammography centers and use of displacement techniques are needed to adequately visualize breast tissue in the implanted breast.

Presurgical mammography with a follow-up mammogram 6 months to 1 year following surgery may be performed to establish a baseline for future routine mammography.

3. ***Radiation to the Breast***

Mentor has not tested the in vivo effects of radiation therapy in patients who have breast implants. The literature suggests that radiation therapy may increase the likelihood of capsular contracture, necrosis, and extrusion.

4. ***Long-Term Effects***

The long-term safety and effectiveness of Mentor implants have not been established. Mentor is monitoring the long-term (i.e., 10-year) risk of implant rupture, reoperation, implant removal, and capsular contracture.

5. ***Instructions to Patients***

- **Reoperation** – Patients should be advised that additional surgery to their breast and/or implant will be likely over the course of their life.
- **Explantation** – Patients should be advised that implants are not considered lifetime devices and they will likely undergo implant removal, with or without replacement, over the course of their life. Patients should also be advised that the changes to their breast following explantation are irreversible.
- **Mammography** – Patients should be instructed to inform their mammographers about the presence, type and placement of their implants. Patient should be advised to request a diagnostic mammography, rather than a screening mammography.
- **Lactation** – Patients should be advised that breast implants may interfere with the ability to successfully breast feed.
- **Infection** – Signs of acute infection reported in association with breast implants include erythema, tenderness, fluid accumulation, pain and fever. In rare instances, Toxic Shock Syndrome (TSS) has been noted in women after breast implant surgery, and it is a life-threatening condition. Symptoms of TSS occur suddenly: a high fever (102°F, 38.8°C or higher), vomiting, diarrhea, a sunburn-like rash, red eyes, dizziness, lightheadedness, muscle aches and drops in

blood pressure which may cause fainting. Patients should be advised to contact a physician immediately for diagnosis and treatment for any of these symptoms.

- **Avoiding Damage During Treatment** – Patients should be instructed to inform other treating physicians of the presence of implants to minimize the risk of damage to the implants.
- **Smoking** – Patients should be informed that smoking may interfere with the healing process.
- **Cosmetic Dissatisfaction** – Patients should be informed that dissatisfaction with cosmetic results related to such things as scar deformity, hypertrophic scarring, asymmetry, displacement, incorrect size, unanticipated contour, and palpability may occur. Careful surgical planning and technique can minimize, but not preclude, the risk of such results. Preexisting asymmetry may not be entirely correctable. Physiological and behavioral differences among patients and variations in surgical techniques and medical treatments account for a wide variety of responses to silicone-filled breast implant surgery. Revision surgery may be indicated to maintain patient satisfaction, but carries additional considerations and risks.
- **Breast Examination Techniques** - Patients should be instructed to perform breast self-examinations monthly and be shown how to distinguish the implant from their breast tissue. The patient should be instructed not to manipulate (i.e., squeeze) the implant excessively.
- **Follow-up Examinations**- Patients should be instructed to have follow up examinations on an annual or biannual basis.

6. ***Rupture***

- If there is a clinical suspicion of rupture, consideration should be given to performance of a Magnetic Resonance Imaging (MRI) examination. If rupture is confirmed by any means, explantation is recommended.

VI. DEVICE DESCRIPTION

The Mentor Silicone Gel-Filled Breast Implants are silicone elastomer mammary prostheses. The gel-filled shell is constructed of successive cross-linked layers of silicone elastomer, which gives the prosthesis its elasticity and integrity. The shell may be smooth or Siltex® (textured).

The breast implant styles are as follows:

Catalog #	Surface	Shape	Profile	Sizes
SILICONE GEL-FILLED BREAST IMPLANTS				
350-7XXXBC	Smooth	Round	Moderate	100-800cc
354-XXX7	Siltex® textured	Round	Moderate	100-800cc
350-XXX1BC	Smooth	Round	Moderate Plus	100-800cc
354-XXX1	Siltex® textured	Round	Moderate Plus	100-800cc
350-XXX4BC	Smooth	Round	High Profile	125-800cc
354-4XXX	Siltex® textured	Round	High Profile	125-800cc

All implants are provided sterile. All implants are sterilized by dry heat. The devices have an expiration date of five years.

VII. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative treatments include, but are not limited to: saline-filled mammary prostheses, external prostheses; autogenous tissue grafts; tissue flaps (e.g., transverse rectus abdominis muscle, latissimus dorsi muscle, gluteal muscle), or no treatment.

VIII. MARKETING HISTORY

Silicone gel-filled breast implants are preamendment devices and have been on the market since the 1960's. Mentor Corporation began marketing silicone gel-filled breast implants in 1984. The Mentor silicone gel-filled breast implants have been available for reconstruction and revision purposes as part of the Mentor adjunct clinical study since 1992.

IX. POTENTIAL ADVERSE EFFECTS

The following is a list of potential adverse effects that may occur with any breast implant surgery. The risks include: implant rupture/leakage, additional surgery, capsular contracture, infection, Toxic Shock Syndrome, necrosis, hematoma, seroma, extrusion, breast pain, changes in nipple sensation, changes in breast sensation, dissatisfaction with cosmetic results (wrinkling, folding, displacement, asymmetry, palpability, visibility, ptosis), calcific deposits, irritation/inflammation, delayed wound healing, hypertrophic scarring, breast tissue atrophy/chest wall deformity, difficulty/inability in breast feeding, and inability to adequately visualize breast lesions with mammography.

In addition to these potential adverse effects, there have been concerns with certain systemic diseases.

Connective Tissue Disease

Concern over the association of breast implants with the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. A review of several large epidemiological studies of women with and without implants indicates that these diseases are no more common in women with implants than in women without implants.

Cancer

Published studies indicate that breast cancer is no more common in women with implants than those without implants.

Second Generation Effects

There have been concerns raised regarding potential damaging effects on children born of mothers with implants. A review of the published literature on this issue suggests that the information is insufficient to draw definitive conclusions

X. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility Data

Biocompatibility testing on raw materials and finished devices or components from finished devices has been provided. Cytotoxicity, acute systemic toxicity, hemocompatibility, and genotoxicity were performed on finished devices or extracts from finished devices using current gel and shell elastomer materials. The devices passed each of the tests. Immunotoxicity, reproductive toxicity, teratogenicity, and carcinogenicity were performed using silicone materials from prior vendors. The silicone materials from prior vendors have been shown to be not substantially different to the current materials now in use. For that reason, the testing was not repeated using the current materials.

Immunotoxicity Studies: A series of studies on Mentor's smooth and textured silicone gel-filled breast implant shells and Dow Corning gel have demonstrated that when implanted for 10 days to as long as 180 days (in one test) the materials did not alter the immune system of mice. No biologically relevant adverse effects were noted. In a related study, using the blood from mice from an immunological study of Mentor's smooth silicone gel-filled shells, no significant differences were noted in serum autoantibody levels of mice with or without the shell implants. No significant differences were found in interferon-gamma levels among mouse groups (with multiple doses of shell implants), nor were any other tested serum cytokine levels detected in any group.

Studies from the literature have shown that silicone gel can provoke a cell-mediated response only when administered under extraordinary conditions. One study has shown that silicone gel can act as an adjuvant in rats while others have demonstrated that only when silicone gel is mixed or emulsified with the antibody can the gel act as an adjuvant. In the clinical setting, it is unlikely that this mixing of gel and antigen in an emulsion-like form would occur. None of these studies has suggested that silicone elastomer has adjuvant activity or any ability to stimulate the immune system. Silicone elastomer particles containing some of the materials found in Mentor's Silicone Gel-Filled Breast Implant shells were reported to have no apparent adjuvant effect in rats, using the same test model as that in which the gel adjuvant effect was observed.

Teratology and Reproductive Toxicity Studies: Mentor has conducted a two generation study in rats to assess the teratogenic and reproductive toxicity potential of Mentor's Silicone Gel-Filled Breast Implant shell. In order to exaggerate the dose of potentially extractable materials the elastomeric test material was pulverized prior to implantation, thus vastly increasing the exposed surface area. The findings of this study indicated that, compared to the controls, pulverized patched and/or valved silicone elastomer mammary prosthetic shells did not cause reproductive or teratogenic effects when implanted subcutaneously in female rats in two consecutive generations. A former vendor has conducted reproduction and teratology studies in rats and rabbits on silicone gel not substantially different from Mentor's current gel. The results indicated that there were no treatment-related effects on F_0 parental general conditions and reproductive performance, F_1 neonatal viability, or growth in the rat reproduction study, and no maternal or developmental effects in the rabbit developmental toxicity study. These results are consistent with published data that shows silicone materials are neither reproductive toxicants nor teratogens in animals.

Genotoxicity Testing: Mentor has conducted mutagenicity testing on finished sterilized Silicone Gel-Filled Breast Implants. Five assays were conducted with extracts of Silicone Gel-Filled Breast Implants (cut open to expose the shell and gel) including: bacterial mutagenicity (Ames), DNA damage (unscheduled DNA synthesis in mammalian cells), chromosome aberrations (chromosome aberrations in Chinese Hamster Ovary cells), mouse lymphoma assay, and in vivo micronucleus assay. The results from each of these assays were negative, indicating a lack of genotoxic activity. These findings are consistent with genotoxicity investigations found on silicone gel-filled breast implants in the literature.

Acute and Subchronic Toxicity Studies: Mentor and its material vendors have completed a broad battery of acute toxicity testing on raw materials, components, and finished sterilized devices. Such testing has included irritation tests, sensitization tests, cytotoxicity, acute systemic toxicity, blood compatibility, pyrogenicity (material-mediated), and implantation tests. The results from these studies have consistently demonstrated a lack of acute toxicity.

Chronic Toxicity and Carcinogenicity Testing: Mentor has conducted a two-year bioassay in rats to evaluate the chronic toxicity and carcinogenicity potential of Mentor's textured and smooth Silicone Gel-Filled Breast Implant shell. In order to exaggerate the dose of potentially extractable materials the elastomeric test material was pulverized prior to implantation, thus vastly increasing the exposed surface area. The materials associated with these Silicone Gel-filled Breast Implant shells did not produce chronic systemic toxicity. Various degrees of inflammatory responses were

observed at the site of implantation. Carcinogenicity was limited to the development of implant site related sarcomas, primarily fibrosarcomas, and their subsequent effects. The presence of fibrosarcomas at the implant sites represents a neoplastic response commonly observed in rodents following the subcutaneous implantation of a broad range of foreign materials As discussed in the literature review section on the potential carcinogenicity of silicone, solid-state carcinogenesis observed in rodents is not considered relevant to human risk. Furthermore, strong epidemiological evidence from at least two large studies involving women with mammary prostheses indicate that there is no increased risk of breast cancer associated with these devices.

Mentor's previous vendor of silicone gels have been tested for chronic toxicity/carcinogenicity. Mentor's current gel has been shown to be not substantially different from the previous vendor's gel. During the chronic toxicity testing, the only abnormal finding was the occurrence of implant site fibrosarcomas and their subsequent effects. Dow Corning's most recent test involving 700 animals definitively demonstrates that silicone gel from mammary prosthesis does not contain a chemical carcinogen.

The result of the chronic toxicity/carcinogenicity testing on Mentor's Silicone Gel-Filled Breast Implant shells and silicone gel, and considering the data from publicly available literature, the components of sterile gel-filled breast implants do not cause adverse systemic effects when implanted in rats. Rats did exhibit expected solid state tumors which are not considered relevant to humans.

Biocompatibility Data Conclusion:

Taken together, the results from Mentor's broad battery of biological/toxicological testing, along with a review of information from available literature, confirms the biological safety of Mentor's Silicone Gel-Filled Breast Implants for their intended use.

B. Chemistry Data

Chemical testing has been performed to characterize Mentor's Silicone Gel-Filled Breast Implant and its major components (shell and gel). Testing was performed in conformance with FDA's Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA (February 11, 2003). The data were used for a toxicity risk analysis of the chemical compounds extracted from the device, verification that certain manufacturing changes did not cause significant changes in the chemical extractables profile of the device, and to support Mentor's conclusion that long term biological safety testing performed on silicone gel-filled breast implants and components made with other silicone vendor materials is still directly applicable to the devices in this PMA submission.

The chemical testing consisted of a total extractables quantitation coupled with detailed qualitative and quantitative analyses of the volatile and semivolatile compounds, and a mostly qualitative nonvolatile extractables analysis. The analytical techniques utilized included gravimetry for overall extractables, dynamic headspace purge/trap with gas chromatography/mass spectroscopy (P/T-GC/MS) for volatiles, direct liquid injection gas chromatography/mass spectroscopy (GC/MS) for semivolatiles, and liquid injection gel permeation chromatography (GPC) for nonvolatiles. Compounds up to 1500 molecular weight were targeted for identification and quantitation.

In addition to the extract testing, determination of extractable heavy metals by inductively coupled plasma/mass spectroscopy, device component crosslink densities, and surface composition analysis by Fourier transform infrared spectroscopy were conducted. Where necessary a solvent extraction comparison and verification of exhaustive solvent extraction were performed. All sample preparation and analysis methods were validated by including spiked recovery of selected analytes

and assessment of quantitation methods for linearity, precision, and detection limits. Reference libraries of standard compounds were developed from consideration of raw materials, additives, synthesis byproducts and manufacturing process aids and were used for positive identification of extractable compounds.

Total Extractables:

The total methylene chloride extractables (as a percentage of the device part) for textured device components and the whole textured device are the following:

Device Part	Total Extractables (% of device part)
Non-gelled Shell	1.9
Shell (from the device)	10.4
Gel Filler	82.7
Whole Device	73.0

Low Molecular Weight Extractable Compounds:

The data reported below are for selected low molecular weight (amu <1500) component extracts from a textured Silicone Gel-Filled Breast Implant

Extractable Compound	Molecular Weight (amu)	Textured Shell (ug/g shell)	Silicone Gel Filler (ug/g gel)
D3	222	0.19	0.18
D4	296	ND	0.5
D5	370	< 2.5	2.5
D6	444	< 4.2	4.9
Isopropanol	60.09	2.03	ND
Xylene	106.2	0.05	0.08
Metals			
Arsenic	74.9	ND	ND
Lead	207.2	0.018	0.010
Platinum	195.1	0.133	0.323
Tin	118.7	ND	ND

Extent of Crosslinking:

Crosslinking was determined by measuring the swell ratio of the shell and gel in toluene and the weight of the non-crosslinked material extracted by the solvent. The data reported below are for components from a textured Silicone Gel-Filled Breast Implant.

Component	Crosslink Density ($mole/cm^3$)	Swell Ratio
Shell	1.31×10^{-4}	3.7
Gel	1.46×10^{-6}	36.9

Device components taken from finished devices were also subjected to an additional post cure to determine whether the crosslink density and the swell ratio changed. The data showed that they did not change, thus demonstrating that the components were completely cured.

Toxicity Risk Analysis:

In addition to the safety testing of the gels and shells, the toxicity risk analysis on the extractable compounds from Mentor Silicone Gel-Filled Breast Implants in this PMA has shown that there are no known compounds extracted from a gel-filled breast implant in a quantity which might pose any toxicological concern when compared to the published toxicity information for those materials.

Chemical Data Conclusion:

The chemical testing data for Mentor's Silicone Gel-Filled Breast Implant PMA strongly supports the biological safety of this device for its intended use and strongly supports the relevance of all the biological testing data in this PMA to Mentor's PMA devices.

C. Mechanical Data

Mentor manufactures silicone gel-filled breast implants that consist of a silicone elastomer shell assembly filled with silicone gel. The devices are available in both smooth and textured surfaces in a round design with three different profiles of varying size. Sterile devices or samples taken from sterile device components representative of devices made using current manufacturing processes were used for the mechanical testing. In addition to the mechanical testing data on the current PMA product, a comparison of physical properties of the current device to Mentor's previous gel-filled devices (made with prior vendor silicone materials) was conducted to support Mentor's conclusion that the long-term biological safety testing performed on older versions of Mentor's gel-filled device shells directly apply to the current devices that are the subject of this PMA

The results of the mechanical testing are summarized below, and demonstrate that Mentor's Silicone Gel-Filled Breast Implants surpass all ASTM specifications.

Shell Testing – All shell testing was performed in accordance with ASTM F 703-96 or ASTM D 624-00.

The results below are averages from multiple lots (including combined sizes)

Shell Test	Specification	Smooth Gel-filled Device	Textured Gel-filled Device
Elongation (%)	≥-------	652	606
Break Force (lbs)	≥--------	6.2	6.9
Tear Resistance (lbs)	----------	2.6	4.8
Patch Adhered Joint Strength[1]	----------	Pass	Pass
Ultimate Joint Strength (lbs)	----------	5.2	6.5
Tension Set (%)	-------	2.7	4.0

[1]Patch Adhered Joint Strength Testing includes--- ---- imate Joint Strength test for information only.

These results indicate that Mentor's Silicone Gel-Filled Breast Implants have high levels of elongation that will aid in withstanding the manipulation and stretching that occurs during surgical placement and stresses applied *in vivo*. The results of these tests also provide evidence that the strength of both shells and joints will aid in resisting failure due to stresses applied during insertion and *in vivo*, and indicate that the shells should resist the propagation of a tear that could result in extruded gel outside of the device shell. Moreover, Mentor's Silicone Gel-Filled Breast Implants have the ability to recover from stretching that could occur during placement and *in vivo*.

Device Gel Bleed Testing – Gel bleed testing of sterile Smooth Moderate Profile Silicone Gel-Filled Breast Implants was performed using the suggested test method in ASTM F703-96, Appendix X2. This method provides a worst case estimate of the amount of silicone gel diffusion through a shell. The results of such testing can be used for "comparison of gel bleed diffusion rates of various product configurations in a laboratory setting" (ASTM F703-96). ASTM standard clearly states, that "The results of this bleed test method can not be correlated with the actual physiological performance of an implant since the chemical gradient is not replicated."

All PMA models use the same materials and design for the shell and gel-filler; as a result, the gel bleed rate measured from one smooth device is indicative of the bleed rate of the other smooth device styles as well. The data obtained in this test demonstrate a relatively low bleed rate

(starting at 0.0035 g/cm^2/week and decreasing to 0.0011 g/cm^2/week at week 15) that became relatively constant after approximately five weeks.

Gel Cohesion Testing - Sterile finished device gel cohesion testing was performed using the ASTM F703-96 Cone/Pendant Gel Test Method and Mentor TM 000366. Specifications for gel cohesivity are set such that the gel mimics the aesthetics of breast tissue while maximizing its tendency to resist flow in the event of a shell rupture. All sizes of all devices tested showed an acceptable gel cohesion measurement indicating that all device gel met the ASTM requirement for being acceptably cured. In-process penetrometer (or texture analyzer) testing determines that any given device lot meets Mentor's requirement for acceptably cured gel. Rheology testing results demonstrate reproducibility of manufacturing process control.

Smooth Gel-filled Device		Textured Gel-filled Device	
Size (cc)	**Mean Gel Cohesion (cm)**	**Size (cc)**	**Mean Gel Cohesion (cm)**
100	----[1]	450	0[2]
250	0		
800	0		

[1]Gel cohesion testing cannot be performed on 100cc devices due to a lack of device gel volume
[2]Mean of multiple lots

Gel cohesivity as determined by gel cohesion testing and penetrometer testing show that the gel meets the appropriate specifications and will help the device mimic actual breast tissue and resist movement of the gel in the event of shell rupture.

Fatigue Testing - Cyclic fatigue testing and compression testing were performed on 100cc Smooth Round Moderate Profile, 100cc Siltex Round Moderate Profile, and 125cc Siltex Round High Profile Breast Implants to represent all silicone gel-filled device types and styles. Compression testing determined the maximum load applied as a single stroke that the device could withstand prior to rupture or failure. Cyclic fatigue testing determined the number of cycles for various load amplitudes at which devices fail or rupture. Applied force versus number of cycles to failure (AF/N) curves were then derived for each device style tested using load amplitudes of 30 – 100 pounds. In addition, the endurance limit, or the load at which a device can endure ten million cycles without failure, was determined for these devices. Finally, the endurance limit was used to determine a safety factor (S_f) by comparing this value to the calculated *in vivo* load experienced by a device during the common fatigue activity of walking.

Compression testing results for devices showed smooth device rupture at a mean of 380 pounds and textured device rupture at a mean of 452 pounds. The smooth and textured gel-filled device endurance limits were 20 and 30 pounds, respectively. Based upon the calculated *in vivo* load on the devices during walking, the implant safety factors for the devices tested were determined to be 5-8 for the largest sizes of the device types and 43-65 for the smallest------- of the device types. All of these safety factors exceed the minimum allowable safety factor ------- that was agreed to with FDA. These data suggest that the *in vitro* endurance limit of the d------- is greater than the estimated *in vivo* load applied to a device during the common fatigue activity of walking.

Device	Size (cc)	Load at Rupture (lbs)	Endurance Limit Load (lb)	Safety Factor[1]
Smooth Rnd. Moderate Profile	100	380	10	21.7
	800	-----	-----	2.7[2]
Siltex Rnd. Moderate Profile	100	452	20	43.5
	800	-----	-----	5.4[2]
Siltex Rnd. High Profile	125	-----	20	35.1
	800	-----	-----	5.4[2]

[1]Safety Factor = Endurance Limit Load/*In Vivo* Load

[2]Assumes 800cc device endurance limit is the same as for 100cc devices

Comparison to Previous Vendor Components - In addition to the mechanical testing data on the PMA device described above, a comparison of PMA device physical properties to Mentor's previous gel-filled devices made with prior vendor silicone components used in long-term biological safety testing was conducted. This comparative testing provides supportive evidence that the long-term biological safety testing performed on prior versions of Mentor's gel-filled device shells directly apply to the current PMA devices. In combination with the chemical extractables profile, extractables quantities of the shells, and manufacturing process data, this physical testing data comparison demonstrated that current shells are physically not substantially different from the prior device shells used in the long-term biological testing and that testing on earlier Silicone Gel-Filled Breast Implants is directly applicable to the current PMA devices.

Conclusion Mechanical Testing

Mechanical tests were conducted in accordance with FDA's "Guidance for Saline, Silicone Gel, and Alternative Breast Implants: Guidance for Industry and FDA" (February 11, 2003), ASTM F703-96, and other tests not included in the previous standards were also performed. The testing performed included shell tensile (ultimate breaking force and elongation), shell tear resistance, patch-to-shell adhered joint testing, shell tension set, static and cyclic fatigue testing, gel cohesivity testing, and finished device gel bleed rate. The results demonstrate that Mentor's Gel-filled Mammary Prostheses surpass standard specification requirements as well as Mentor's own finished product specifications. Based on the data presented in this module, together with a history of safe and effective performance *in vivo*, it can be concluded Mentor's Gel-filled Mammary Prostheses that are the subject of this PMA are mechanically acceptable and safe for their intended use.

XI. SUMMARY OF THE PROSPECTIVE CLINICAL STUDIES

A. Study Design

The safety and effectiveness of the Mentor Silicone Gel-Filled Breast Implants were evaluated in two multi-center clinical studies: the Adjunct Clinical Study and the Core Clinical Study.

The Adjunct Study was designed as a prospective 5-year open enrollment study to assess outcomes for a large number of patients. Patients are those undergoing Primary Reconstruction (reconstructive mammaplasty on a breast that has not undergone prior mammaplasty, following mastectomy or other cancer treatments requiring reconstruction); Revision Reconstruction (correction of complications or unfavorable results of a reconstruction surgery); Revision Augmentation (medically necessary replacement of an existing breast implant originally placed for augmentation, when saline-filled implants are not suitable as a replacement), or Severe Deformity (reconstructive mammaplasty to correct post-trauma deformities, congenital or developmental deformities, severe ptosis correctable by mastopexy, or medical or surgical complications resulting in severe breast deformity). Patients with any of the following are excluded from the study: an active infection or abscess anywhere in the body; pregnancy or nursing mothers; lupus (e.g., SLE and DLE); scleroderma (e.g., progressive systemic sclerosis); uncontrolled diabetes or other disease which impacts healing; tissue characteristics which are clinically incompatible with mammaplasty (e.g., tissue damage resulting from radiation, inadequate tissue, compromised vascularity or ulceration); history of sensitivity to foreign materials or repeated attempts and failures at breast reconstruction or augmentation; possess any condition, or currently be under treatment for any condition, which in the plastic surgeon's and/or consulting physician's opinion, may constitute an unwarranted surgical risk; an unwillingness to undergo any further surgery for revision; psychological characteristics such as inappropriate attitude or motivation which, in the surgeon's opinion, are incompatible with the surgical procedure and prosthesis, augmentation mammaplasty and the failure to have one of the indications listed above. Follow-up visits occur postoperatively at 1, 3 and 5 years. The safety assessment was based on the reported incidence of capsular contracture, seroma, infection and rupture. The secondary objective of the study was to provide data concerning potential complications in addition to those reported in the safety assessment.

The Core Study was designed as a 10-year prospective study of female patients aged 18 years of age or older seeking silicone gel-filled breast implants for Augmentation, Reconstruction, or Revision of an existing implant. Patients with any of the following conditions were excluded from the study: patient is pregnant; has nursed a child within three months of study enrollment; been implanted with any silicone implant other than breast implants; confirmed diagnosis of rheumatic disease; currently has a condition that could compromise or complicate wound healing (except reconstruction patients); patient in augmentation cohort and has diagnosis of active cancer of any type; infection or abscess anywhere in the body; demonstrates tissue characteristics which are clinically incompatible with implant (e.g., tissue damage resulting from radiation, inadequate tissue, or compromised vascularity); possesses any condition, or is under treatment for any condition which, in the opinion of the investigator and/or consulting physician, may constitute an unwarranted surgical risk; anatomic or physiologic abnormality which could lead to significant postoperative adverse events; demonstrates characteristics that are unrealistic/unreasonable with the risks involved in the surgical procedure; untreated or inappropriately treated breast malignancy, without mastectomy; and implanted metal or metal devices, history of claustrophobia or other condition that would make a Magnetic Resonance Imaging (MRI) scan prohibitive.

In the Core Study, the patients' medical histories were collected at baseline. Follow-up visits occur postoperatively at 6 months, 12 months, 24 months, and annually from 3 to 10 years post-implantation. MRI scans to detect silent rupture of the implant for a subset of patients are performed subsequent to the annual visits at 1, 2, 4, 6, 8 and 10 years. Safety assessments include complication rates and rates of reoperation. Effectiveness assessments include patient satisfaction, circumferential chest size change and bra cup size change (augmentation patients only), and measures of patients' quality of life. Patient follow-up in the Core Study is currently ongoing.

B. Patient Accounting and Baseline Demographic Profile

The Adjunct Study enrolled 6,967 Primary Reconstruction patients, 8,986 Revision Reconstruction patients, 25,219 Revision Augmentation patients, and 6,321 Severe Deformity patients. New patient enrollment is ongoing. Of the patients who reached the scheduled 5 year follow-up visit, 13% of Primary Reconstruction patients, 12% of Revision Reconstruction patients, 9% of Revision Augmentation patients, and 7% of Severe Deformity patients returned for their 5 year visit.

The Core Study enrolled 551 augmentation patients, 252 Reconstruction patients, and 205 Revision patients. Data are available for 95% of the eligible Augmentation patients, 92% of the eligible Reconstruction patients, and 92% of the Revision patients at 2 years post-implantation.

Demographic information in the Core Study is as follows. With regard to race, 90% of the Core Study patients were Caucasian, 2% were Asian, 2% were African American, and 6% were other. The mean age at surgery was 34 years for Augmentation patients, 45 years for Reconstruction patients, and 44 years for Revision patients. Most of the Core Study patients were married (56% of the Augmentation patients, 69% of the Reconstruction patients, and 61% of the Revision patients). Approximately 80% had some college education.

With respect to surgical baseline factors in the Core Study, for Augmentation patients, the most frequently used devices were smooth surface implants, the most common incision site was inframammary, and the most frequent site of placement was submuscular. For Reconstruction patients, the most frequently used devices were textured surface implants, the most common incision site was the mastectomy scar, and submuscular placement was the favored site. For Revision patients, the most frequently used devices were smooth surface implants, the most common incision sites were inframammary, and submuscular placement was the favored site.

C. Safety Outcomes for Adjunct Study

The cumulative Kaplan-Meier risk of first occurrence of adverse events (and 95% confidence interval) reported in greater than 1% of patients in the Adjunct Study is shown below.

Adjunct Study 5-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient

Complication	Primary Reconstruction	Revision Reconstruction	Revision Augmentation	Severe Deformity
	Rate (%) (95% CI)	Rate (%) (95% CI)	Rate (%) (95%CI)	Rate (%) (95% CI)
Asymmetry	54 (51, 58)	46 (43, 49)	24 (23, 26)	24 (20, 29)
Reoperation	42 (39 45)	27 (25, 30)	14 (13, 15)	10 (8,12)
Wrinkling	33 (30, 37)	31 (28, 33)	29 (27, 30)	20 (16, 24)
Explantation	29 (26,32)	25 (23,28)	18 (16, 19)	14 (10, 17)
Breast Pain	26 (23,29)	27 (24, 30)	20 (18, 21)	15 (11, 18)
Capsular Contracture III /IV	23 (20, 26)	24 (22, 27)	20 (19, 22)	11 (8 15)
Hypertrophic Scarring	11 (9, 13)	8 (6,9)	6 (5 7)	6 (4,7)
Irritation/Inflammation	6 (4,7)	7 (5,8)	4 (3 5)	3 (1,5)
Infection	5 (3,6)	5 (3,6)	2 (2 3)	3 (1,5)
Delayed Wound Healing	4 (3,5)	3 (2,4)	1 (1,2)	2 (1,2)
Necrosis	3 (2,4)	1 (0,2)	1 (0 1)	1 (0 1)
Extrusion	3 (2,5)	1 (1,2)	1 (1 1)	1 (0,1)
Seroma	1 (1,1)	3 (2,4)	2 (2,3)	1 (0,2)
Hematoma	1 (1,2)	2 (2,3)	3 (2,3)	2 (1,2)
Rupture/Deflation	1 (0,2)	3 (2,4)	1 (1,2)	0 (0,1)
Lymphadenopathy	1 (0,1)	2 (1,3)	2 (2,3)	0 (0,1)
Calcification	1 (0,1)	3 (2,4)	1 (1 2)	0 (1,2)

D. Safety Outcomes for Core Study

Safety outcomes assessed in the Core Study are reported for Augmentation, Reconstruction and Revision in the tables provided below.

1. Cumulative Kaplan-Meier Risk of First Occurrence of Complications

The cumulative Kaplan-Meier risk of first occurrence of complications (and 95% confidence interval) by implant and by patient is shown below.

Core Study 2-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient

Complication*	Augmentation By Patient N=551		Reconstruction By Patient N=252		Revision By Patient N=205	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation	12 1%	(9 4 14 9)	25 2%	(19 8, 30 6)	21 1%	(15 4, 26 7)
Capsular Contracture III/IV	7 9%	(5 6 10 2)	7 3%	(3 9, 10 7)	16 3%	(11 1, 21 4)
Hypertrophic Scarring	6 1%	(4 1, 8 2)	3 9%	(1 0 6 8)	5 7%	(2 4 8 9)
Nipple Sensitivity (Unacceptably High)	6 0%	(4 1, 8 1)	1 6%	(0 05, 3 2)	6 1%	(2 8, 9 5)
Hematoma	2 6%	(1 2, 3 9)	0 8%	(0 0, 1 9)	3 0%	(0 6, 5 4)
Ptosis	2 1%	(0 8, 3 3)	3 6%	(0 0, 7 4)	2 7%	(0, 5 5)
Patient Request for Size Change	2 0%	(0 8, 3 2)	0 8%	(0 0 1 9)	3 1%	(0 7, 5 6)
Infection	1 5%	(0 4 2 5)	5 3%	(2 5, 8 2)	1 0%	(0 0, 2 5)
Miscarriage	1 1%	(0 2, 2 0)	0 8%	(0, 2 0)	0%	(0,0)
Surgical Complications Related to Technique	1 0%	(0 1, 1 9)	2 1%	(0 3, 3 8)	2 0%	(0 06 3 9)
Seroma	0 9%	(0 1 1 7)	4 4%	(1 9, 6 9)	2 0%	(0 06, 3 9)
Breast Mass Not Associated with Implant	0 8%	(0 02 1 5)	2 1%	(0 3 4 0)	3 5%	(1 0, 6 1)
New Diagnosis of Rheumatic Disease	0 4%	(0, 0 9)	0%	(0 0)	1 0%	(0, 2 4)
Inflammation	0 4%	(0 0 9)	0%	(0,0)	1 5%	(0, 3 2)
Granuloma	0 2%	(0, 0 5)	0%	(0 0)	1 0%	(0 0, 2 4)
Size Change Based on Physician Assessment	0%	(0,0)	1 7%	(0 05, 3 3)	0%	(0,0)
Extrusion	0%	(0, 0)	1 6%	(0 05 3 2)	1 5%	(0 0, 3 2)
Recurrent Breast Cancer	0%	(0,0)	1 3%	(0, 2 8)	0 5%	(0, 1 5)
Patient Dissatisfied with Appearance	0 2%	(0,0 6)	0%	(0,0)	1 5%	(0 3 3)
Other (Non-cosmetic)	2 7%	(1 2, 4 2)	7 8%	(4 3, 11 4)	4 4%	(1 4, 7 4)

*Excludes mild occurrences of asymmetry, breast pain, calcification, position change, nipple sensitivity (unacceptably low), breast sensitivity (unacceptably low and unacceptably high), nipple complications, and wrinkling

Core Study 2-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Implant

Complication*	**Augmentation By Implant N=1126**		**Reconstruction By Implant N=388**		**Revision By Implant N=382**	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation	8 9%	(7 3, 10 6)	20 4%	(16 3, 24 5)	16 7%	(12 8, 20 6)
Capsular Contracture III/IV	5 3%	(3 9 6 6)	5 0%	(2 7, 7 3)	10 8%	(7 7, 14 0)
Hypertrophic Scarring	4 7%	(3 4, 5 9)	2 8%	(0 9, 4 8)	5 0%	(2 7 7 2)
Nipple Sensitivity (Unacceptably High)	4 6%	(3 4, 5 8)	1 1%	(0 03, 2 1)	4 9%	(2 7, 7 0)
Hematoma	1 3%	(0 6, 1 9)	0 5%	(0, 1 2)	1 9%	(0 5, 3 2)
Ptosis	1 7%	(0 9 2 6)	1 7%	(0 4, 3 0)	2 6%	(0 6, 4 6)
Patient Request for Size Change	1 9%	(1 1, 2 7)	0 8%	(0, 1 7)	3 1%	(1 3 4 9)
Infection	0 7%	(0 2, 1 2)	3 5%	(1 6, 5 3)	0 6%	(0, 1 3)
Surgical Complications Related to Technique	0 7%	(0 2, 1 2)	1 4%	(0 2, 2 5)	0 5%	(0, 1 3)
Seroma	0 5%	(0 1, 1 0)	2 6%	(1 0, 4 2)	1 1%	(0 03, 2 1)
Breast Mass Not Associated with Implant	0 5%	(0 06, 0 9)	1 1%	(0 03, 2 2)	1 9%	(0 5, 3 3)
Inflammation	0 2%	(0, 0 4)	0	(0,0)	0 5%	(0, 1 3)
Granuloma	0 1%	(0, 0 3)	0	(0,0)	0 5%	(0, 1 3)
Size Change Based on Physician Assessment	0	(0,0)	1 6%	(0 3 2 9)	0	(0,0)
Extrusion	0	(0 0)	1 1%	(0 03 2 1)	0 8%	(0, 1 7)
Recurrent Breast Cancer	0	(0,0)	1 1%	(0 03, 2 2)	0 3%	(0, 0 8)
Patient Dissatisfied with Appearance	0 2%	(0, 0 4)	0	(0,0)	1 7%	(0 3, 3 0)
Other (Non-cosmetic)	1 4%	(0 7, 2 2)	3 7%	(1 7 5 7)	2 0%	(0 5, 3 6)

*Excludes mild occurrences of asymmetry, breast pain, calcification, position change, nipple sensitivity (unacceptably low), breast sensitivity (unacceptably low and unacceptably high), nipple complications, and wrinkling

2. Types of Reoperations Through 2 Years

The tables below show the types of reoperations performed through 2 years postoperatively in the Core Study based on the number of reoperations.

Core Study Types of Reoperations through 2 Years for Augmentation
Of the 551 augmentation patients, there were 66 (12%) who underwent at least one reoperation over the 2 years of follow-up in the Core Study A total of 114 reoperations were performed in augmentation patients over the 2 years of the Core Study The types of reoperations are shown below based on the number of reoperations

Types of Reoperations for Augmentation	N = 114 procedures	
	n	%
Capsulectomy	32	28 1
Open Capsulotomy	17	14 9
Implant Size Change	16	14 0
Scar Revision	15	13 2
Incision and Drainage	12	10 5
Implant Removal without Replacement	10	8 8
Skin Adjustment	5	4 4
Biopsy	4	3 5
Implant Removal with Replacement (other than size change)	4	3 5
Position Change	4	3 5
Capsulorrhaphy	4	3 5
Revision of Wound Closure	3	2 6
Mastopexy	2	1 8
Closed Capsulotomy	2	1 8
Implant Pocket Revision	2	1 8
Other	3	2 6
TOTAL	**114**	**100%**

Core Study Types of Reoperations through 2 Years for Reconstruction
Of the 252 reconstruction patients in the Core Study 62 (25%) underwent at least one reoperation over the 2 years of follow-up A total of 87 additional surgical procedures were performed in reconstruction patients over the 2 years The types of reoperations are shown below based on the number of procedures

Types of Reoperations for Reconstruction	N = 87 procedures	
	n	%
Implant Size Change	18	20 7
Position Change	17	19 5
Open Capsulotomy	16	18 4
Skin Adjustment	13	14 9
Capsulectomy	12	13 8
Implant Removal (without Replacement)	11	12 6
Biopsy	9	10 3
Implant Removal With Replacement (other than size change)	7	8 0
Scar Revision	7	8 0
Implant Pocket Revision	6	6 9
Mastopexy	4	4 6
Incision and Drainage	3	3 4
Revision of Wound Closure	2	2 3
Capsulorrhaphy	2	2 3
Other	7	8 0
TOTAL	**87**	**100**

Core Study Types of Reoperations through 2 Years for Revision
Of the 204 revision patients in the Core Study, 42 (21%) underwent at least one reoperation over the 2 years of follow-up A total of 85 reoperations were performed in revision patients over the 2 years The types of reoperations are shown below based on the number of procedures

Types of Reoperations for Revision	N =85 procedures	
	n	%
Implant Size Change	15	17 6
Capsulectomy	14	16 5
Open Capsulotomy	12	14 1
Skin Adjustment	12	14 1
Implant Removal (Without Replacement)	9	10 6
Biopsy	8	9 4
Position Change	8	9 4
Incision and Drainage	7	8 2
Capsulorraphy	6	7 1
Closed Capsulotomy	6	7 1
Scar Revision	6	7 1
Mastopexy	4	4 7
Implant Removal With Replacement (other than size change)	2	2 4
Revision of Wound Closure	2	2 4
Implant Pocket Revision	1	1 2
Other	5	5 9
TOTAL	**85**	**100**

3. Reasons for Removal/Replacement Through 2 Years

The primary reason for implant removal is shown in the following tables, based on the total number of implants removed.

Core Study Reasons for Implant Removal through 2 Years for Augmentation
Of the 551 augmentation patients, there were 18 patients (3%) who had 30 implants removed over the 2 years of follow-up in the Core Study Of the 30 augmentation implants removed, 66% were replaced The reason for implant removal is shown in the table below based on the number of implants removed

Reason for Implant Removal through 2 Years for Augmentation	N = 30 Implants Removed	
	n	%
Size Change	18	60%
Breast Pain	2	7%
Capsular Contracture (III and IV)	2	7%
Infection	2	7%
Wrinkling	1	3%
Other	5	17%
Total	**30**	**100%**

Core Study Reasons for Implant Removal through 2 Years for Reconstruction
Of the 252 reconstruction patients there were 28 patients (11%) who had 35 implants removed over the 2 years of follow-up in the Core study Of the 35 reconstruction implants removed, 72% were replaced The reason for implant removal is shown in the table below based on the number of implants removed

Reason for Implant Removal through 2 Years for Reconstruction	N = 35 Implants Removed	
	n	%
Size Change	8	23%
Asymmetry	8	23%
Position Change	5	14%
Capsular Contracture (III and IV)	3	9%
Infection	2	6%
Extrusion	2	6%
Hematoma	1	3%
Other	6	17%
Total	**35**	**100%**

Core Study Reasons for Implant Removal through 2 Years for Revision
Of the 205 revision patients there were 17 patients (8%) who had 26 implants removed over the 2 years of follow-up in the Core study Of the 26 revision implants removed, 65% were replaced The reason for implant removal is shown in the table below based on the number of implants removed

Reason for Implant Removal through 2 Years for Revision	N = 26 Implants Removed	
	n	%
Size Change	8	31%
Capsular Contracture (III and IV)	5	19%
Asymmetry	3	11%
Extrusion	2	8%
Hypertrophic Scarring	1	4%
Infection	1	4%
Other	6	23%
Total	**26**	**100%**

4. CTD and Breast Disease

There were a total of two patients (0.2%) who were newly diagnosed with breast cancer through 2 years postimplantation. The incidence of recurrence of breast cancer and of breast mass are shown in the Cumulative Kaplan-Meier Risk of First Occurrence of Complications tables in Section XI.D.1 above.

Connective Tissue Disease (CTD) was reported in some Core Study patients through 2 years. These data should be interpreted with the precaution in that there was no comparison group of similar women without implants. The table below summarizes post-implant observations from the Core Study pertaining to confirmed reports of CTD that were based on a diagnosis by a physician.

Core Study Number of Confirmed Reports of CTD through 2 Years, By Patient

Rheumatic Disease	Augmentation Patients	Reconstruction Patients	Revision Patients
Hashimoto Thyroiditis	1	0	0
Fibromyalgia	0	1	1
Pyoderma Gangrenosum	0	0	1
Rheumatoid Arthritis	1	0	0
Other Thyroiditis	1	0	0
TOTAL	3	1	2

E. Effectiveness Outcomes for Core Study

Effectiveness was assessed based primarily on changes in circumferential breast size and bra cup size, and secondarily, based on changes in the results of quality of life questionnaire results and global patient satisfaction. The Tennessee Self-Concept Scale (TSCS), the SF-36 Health Survey Scale, the Bode Esteem Scale, the Rosenberg Self-Esteem Scale, the Manitoba Cancer Treatment & Research Foundation Functional Living Index: Cancer (FLIC) (cancer patients only), and Global Patient Satisfaction were used to assess effectiveness. Global patient satisfaction was assessed by whether the patient would have the surgery again.

Implantation of the Mentor Silicone Gel-Filled Breast Implants resulted in a significant increase in circumferential chest size and bra cup size in augmentation patients, and restoration of the chest mound in reconstruction and revision patients. For patients overall, and for all indications, the changes in circumferential breast size were positive and highly significant. The average increase in circumferential breast size for patients overall was 5.5 cm. The average increase in circumferential breast size was 7.0 cm for augmentation patients, 3.2 cm for reconstruction patients, and 2.8 cm for revision patients.

Among augmentation patients, greater than 97% had an increase in bra cup size of at least one step (e.g., from A to B cup size) at each of the various follow-up visits. The overall average increase in breast cup size was 1.7 cup sizes

The results of the Tennessee Self-Concept Scale (which measures self-concept) showed that there was a decrease across follow-up visits among revision patients, indicating a lowering of their overall level of self-esteem. The changes for augmentation patients and reconstruction patients were not significant. When the total score of Tennessee Self-Concept Scale was analyzed by device placement, for submuscular placement, a statistically significant overall mean increase was observed for augmentation patients, no significant difference was observed for reconstruction patients, and a statistically significant overall mean decrease was observed for revision patients.

On the SF-36 Health Survey, at baseline, the overall population scored significantly higher than did the general United States female population on all eight subcategories. The study patients also scored significantly higher than the United States female population on the Mental Component Score (MCS) and Physical Component Score (PCS). The results for some of the subscales showed scores that decreased slightly, but statistically significantly, from preoperative to postoperatively, indicating a slight worsening in physical and mental health. However, the magnitude of these changes was slight, and postoperatively the study patients continued to score statistically higher for all

eight subcategories and the MCS and PCS as compared to the United States female population.

The results of the Body Esteem Scale showed there was no significant change in body esteem among the augmentation and reconstruction patients. Among revision patients, there was a statistically significant decrease, indicating a worsening of body esteem in revision patients.

The Rosenberg Self-Esteem Scale showed significant overall mean increases in augmentation patients, indicating improvement in self-esteem. There were no changes among the reconstruction patients and revision patients.

The Functional Living Index: Cancer (FLIC) showed a significant overall mean increase in delayed post-mastectomy patients, indicating a higher level of functioning.

Global Patient Satisfaction indicated that, at the 2-year follow-up visit, 98% of patients said they would have the implant surgery again. The results were similar for Augmentation patients (99%), Reconstruction patients (97%) and Revision patients (95%). Furthermore, 96% of patients who had a reoperation indicated that they would have breast implant surgery again.

XII. SUMMARY OF OTHER CLINICAL INFORMATION

A. Literature Summary of Potential Systemic Diseases

CTD/Adverse Immunological Events

The Institute of Medicine (IOM) expert panel reviewed the very extensive body of information on this issue and focused in their report on the findings of epidemiological investigations of this issue. Their review addressed both defined connective tissue or rheumatic diseases, as well as atypical connective tissue or rheumatic disease. With respect to defined, or typical connective tissue disorders, the IOM expert panel reported that:

"The committee concludes that there is insufficient evidence to support an association of silicone breast implants with defined connective tissue disease. That is, given the repeated finding of no elevated risk, the evidence supports the conclusion that there is no association, and therefore no justification for the use of resources in further epidemiological exploration of such an association."

Information from several well-designed, population-based epidemiological studies published subsequent to the IOM expert panel review, as a whole, also find no association between such signs and symptoms and silicone mammary prostheses, whether intact or ruptured.

Cancer

Evidence continues to accumulate from a number of large well-controlled epidemiological studies that silicone gel-filled breast implants are not associated with any elevated risk of breast cancer. The Institute of Medicine (IOM) expert panel reviewed the body of scientific evidence on the overall issue of cancer and silicone breast implants and concluded in its report that the available evidence does not support an association of silicone or silicone breast implants with cancer. The findings led two authors of a recently published review of silicone breast implants and cancer (from the Institute of Medicine and the Memorial Sloan-Kettering Cancer Center) to note that: "We concluded from our review that, overall, medical and surgical oncologists have no reason for concern about possible relationships of silicone breast implants with any experimental or

clinical malignancies. An impressive body of evidence has failed to find a convincing association of these implants with cancer in women."

Implants, Breast Feeding and Effects on Children

The IOM expert panel evaluated the body of available data on the issues of potential health effects on offspring. It concluded that the evidence for an association between maternal silicone breast implants and children's health effects, including esophageal disease, was insufficient or flawed, and that no biologically plausible causation has been suggested.

The conclusions of the IOM expert panel have been further strengthened by the subsequent publication of two additional, large, well-controlled, population-based epidemiological studies (one from Sweden and an expanded one from Denmark) that found no evidence to support an association of maternal silicone breast implants and adverse health outcomes, including congenital malformations, in offspring.

The IOM expert panel report detailed three studies that focused on augmentation mammaplasty and effects on lactation sufficiency, each of which identified periareolar incisions as a significant risk factor for lactation insufficiency. In the first study, periareolar incisions among breast surgery patients were found to be five times more likely to be associated with lactation insufficiency. In a second study, seven out of eight women with lactation insufficiency had periareolar incisions. All eleven patients in a third study who had periareolar incisions experienced lactation insufficiency. The available information continues to suggest that surgical procedure, rather than the breast implants themselves, represents a significant risk factor for lactation insufficiency. Such findings are not surprising, given that the transglandular trajectory typically associated with this surgical approach would be expected to disrupt ductal tissue.

B. MDR [Pending from FDA]

XIII. PANEL RECOMMENDATION

To be determined

XIV. CDRH DECISION

To be determined.

XV. APPROVAL SPECIFICATIONS

To be determined